WHAT IS CLAIMED:

1. A polypeptide comprising,

SAGDMRAANL WPSPLMIKRS KKNSLALSLT ADQMVSALLD
AEPPILYSEY DPTRPFSEAS MMGLLTNLAX$_1$ RELVHMINWA
KRVPGFVDLT LHDQVHLLEC AWMEILMIGX$_2$ VWRSMEHPGK
LLX$_3$APNLLLD RNQGKCVEGX$_4$ VEX$_5$FDMX$_6$LAT SSRFRMMNLQ
GEEFVCLKSI ILLNSGVYTF LSSTLKSLEE KDHIHRVLDK
ITDTLIHLMA KAGLTLQQQH QRLAQLLLIL SHIRHMSNKX$_7$
MEX$_8$LYSMKCK NVVPLYDLLL EMLDAHRLHA PTSRGGASVE
ETDQSHLATA GSTSSHSLQK YYITGEAEGF PATV

wherein X_1 = D or A; X_{2-6} are each independently G, A, C, V, I, L; M, F, Y, or W; X_7 = G or R; and X_8 = H or V.

2. The polypeptide of claim 1 wherein X_2 = L, M, or V; X_3 = F or W; X_4 = M, G or A; X_5 = I, M, V, or L; X_6 = L.

3. The polypeptide of claim 2 wherein X_1 = D; X_7 = G; and X_8 = H.

4. The polypeptide of claim 3 comprising the amino acid sequence of SEQ ID NO: 2.

5. The polypeptide of claim 3 wherein X_4 = G or A.

6. The polypeptide of claim 5 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3-15.

7. The polypeptide of claim 2 wherein X_1 = A, X_4 = G or A; X_7 = G, and X_8 = V.

8. The polypeptide of claim 7 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 16-28.

9. The polypeptide of claim 2 wherein X_1 = D, X_4 = G or A; X_7 = R, and X_8 = H.

10. The polypeptide of claim 9 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 29-41.

11. A polynucleotide encoding the polypeptide of claim 1.

12. A transcription factor comprising,
a DNA-binding domain,
a ligand-binding domain comprising the polypeptide of claim 1, and
a transcription regulatory domain.

13. The transcription factor of claim 12 wherein the ligand-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 16-41.

14. The transcription factor of claim 12 wherein the DNA-binding domain is GAL4 minimal DNA-binding domain.

15. The transcription factor of claim 12 wherein the DNA-binding domain is the DNA-binding domain of HNF-1.

16. The transcription factor of claim 12 wherein the transcription regulatory domain is VP16 minimal activation domain.

17. The transcription factor of claim 12 wherein the transcription regulatory domain is a portion of the activation domain of human p65.

18. The transcription factor of claim 12 comprising SEQ ID NO: 43.

19. A polynucleotide encoding the transcription factor of claim 12.

20. A host cell transformed with a composition comprising the polynucleotide of claim 18.

21. A compound that binds to and activates the transcription factor of claim 12.

22. The compound selected from the group consisting of CMP1 and CMP4-38.

23. An orthogonal gene switch for regulating the expression of a desired gene, the gene switch comprising, the transcription factor of claim 13; and a vector comprising the desired gene, and a regulatory region that is fused to the desired gene, wherein the transcription factor is capable of binding to the regulatory region.

24. The gene switch of claim 23 further comprising a compound that binds to the ligand-binding domain and activates the transcription factor.

25. The gene switch of claim 24 wherein the ligand-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 16-28, and the compound is selected from the group consisting of CMP1, CMP4, CMP5, and CMP11-38.

26. The gene switch of claim 23 wherein the ligand-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 29-41, and the compound is selected from the group consisting of CMP6-10.

27. A method of making an orthogonal gene switch, the method comprising:

selecting a ligand-binding domain (LBD) from a nuclear hormone receptor;
selecting an inactive analogue of the hormone; constructing a library of transcription factors comprising veneered variants of the selected LBD, which are created by mutating amino acid residues that hinder the binding of the selected inactive analogue to various amino acid residues that might facilitate the binding; and screening the library with the selected inactive analogue to select the transcription factors that are activated by the inactive analogue.

28. The method of claim 27 further comprising introducing mutations into the veneered LBDs of the selected transcription factors to reduce their affinity to the hormone and the ligand-independent activity of the transcription factors.

29. The method of claim 28 further comprising making inactive analogues that are capable of activating the transcription factors carrying the mutations.

30. The method of claim 27 wherein the nuclear hormone receptor is selected from the group consisting of estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR),

mineralocorticoid receptor (MR), progesterone receptor (PR), vitamin D_3 receptor (VDR), thyroid hormone receptor (TR), and retinoic acid receptor (RAR).

31. The method of claim 29 wherein the nuclear hormone receptor is human estrogen receptor α (hERα).

32. The method of claim 30 wherein the ligand-binding domain comprising SEQ ID NO: 2.

33. The method of claim 27 wherein the inactive analogue is an inactive analogue of a nuclear hormone receptor-specific agonist or antagonist.

34. The method of claim 33 wherein the inactive analogue is an inactive analogue of hERα-specific agonist or antagonist.

35. The method of claim 33 wherein the inactive analogue is an inactive analogue of a human estrogen receptor β (hERβ)-specific agonist or antagonist.

36. The method of claim 35 wherein the inactive analogue is CMP1.

37. The method of claim 27 wherein the library is a yeast one hybrid system.

38. The method of claim 27 wherein the transcription factor further comprising a GAL4 minimal DNA-binding domain (DBD) and a VP16 minimal activation domain (AD).

39. The method of claim 32 wherein the library of transcription factors contains veneered LBDs with their amino acid residues 391, 404, 421, 424, and 428 independently selected from the group consisting of Gly, Ala, Cys, Val, Ile, Leu, Met, Phe, Tyr, and Trp.